Check for updates

Received: 9 August 2023 | Revised: 12 October 2023 | Accepted: 18 January 2024

DOI: 10.1111/sji.13361

Scandinavian Journal of Immunology An International Monthly Journal WILEY

REVIEW

The role of bile acid receptor TGR5 in regulating inflammatory signalling

Daijiao Ye[1] | **Jiayao He**[1] | **Xiaofei He**[1,2]

[1]Medical Research Center, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang Province, China

[2]The Key Laboratory of Pediatric Hematology and Oncology Disease of Wenzhou, The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Wenzhou, Zhejiang Province, China

Correspondence
Xiaofei He, Biomedicine Research Center, Wenzhou Medical University, 1 Xuefubei Street, Ouhai District, Wenzhou, Zhejiang Province, China.
Email: hexiaofei_zg@163.com

Funding information
First Affiliated Hospital of Wenzhou Medical University Fund Project, Grant/Award Number: 2022QD040

Abstract

Takeda G protein-coupled receptor 5 (TGR5) is a bile acid receptor, and its role in regulating metabolism after binding with bile acids has been established. Since the immune response depends on metabolism to provide biomolecules and energy to cope with challenging conditions, emerging evidence reveals the regulatory effects of TGR5 on the immune response. An in-depth understanding of the effect of TGR5 on immune regulation can help us disentangle the interaction of metabolism and immune response, accelerating the development of TGR5 as a therapeutic target. Herein, we reviewed more than 200 articles published in the last 20 years in PubMed, to discuss the roles of TGR5 in regulating inflammatory response, the molecular mechanism, as well as existing problems. Particularly, its anti-inflammation effect is emphasized.

KEYWORDS

anti-inflammatory, chemical modulators, immunotherapy, molecular mechanism, TGR5

1 | INTRODUCTION

Takeda G protein-coupled receptor 5 (TGR5), also named as G protein-coupled bile acid receptor 1 (GPBAR1) or G protein-coupled receptor 19 (GPCR19 or GPR131), is a membrane receptor (M-BAR) of bile acids (BAs).[1] Its gene has one exon that encodes seven transmembrane domains, which consist of 330 amino acids.[2,3] TGR5 belongs to the largest cell membrane receptor GPCR family,[4] and approximately 30%–50% of all pharmaceuticals on the market today exert their therapeutic effects by interacting with GPCRs.[5] Besides, the *GPBAR1* gene sequence is highly conserved among vertebrates suggesting its physiological importance.[6] Therefore, the druggability of TGR5 has attracted much attention in the last two decades.

TGR5 is crucial for biliary homeostasis by working together with other BA receptors. TGR5 and farnesoid X receptor (FXR) are the two most characterized receptors that have a relatively high affinity to BAs.[7] Unlike FXR, a nuclear protein, that is activated by primary BAs, TGR5 is activated by all known BAs regardless of their conjugation status.[8] TGR5 has a high binding affinity to secondary BAs, that is, lithocholic acid (LCA) and deoxycholic acid (DCA), as well as their taurine and glycine derivatives.[9–12] Taurolithocholic acid (TLCA) is the most potent endogenous agonist for TGR5, and TGR5 responds to BAs in the order of TLCA > LCA > DCA > chenodeoxycholic acid (CDCA) > cholic acid (CA).[13,14]

TGR5 regulates metabolism by affecting fat intake, lipid digestion[15] and glucose metabolism,[16] as well as promoting mitochondrial fission, remodelling white adipose tissue and increasing energy expenditure in brown adipose tissue.[17] Thus, the activation of TGR5 by natural bile acids or synthetic agonists reduced weight gain.[18,19] The

© 2024 The Scandinavian Foundation for Immunology.

deletion of the *Gpbar1* gene in mice increased the susceptibility to developing insulin resistance, hyperlipidaemia, liver steatosis and obesity.[20] In addition, accumulating but sporadic evidence identifies the function of TGR5 in regulating immune response in various organs. Herein, we summarize the anti-inflammatory effects of TGR5 in different tissues based on PubMed publications and take the digestive tract as an example to clarify the detailed mechanisms, aiming to accelerate the exploration of TGR5 as a therapeutic target.

2 | TGR5 IS HIGHLY EXPRESSED IN IMMUNE CELLS

TGR5 is ubiquitously expressed in tissues, represented by gallbladder, adipose tissue, smooth muscle, breast, spleen and placenta.[21] During tumorigenesis, TGR5 expression was reduced in most tumours but increased in acute myeloid leukaemia and pancreatic adenocarcinoma.[22] Specifically, TGR5 has high expression in monocytes, natural killer (NK) cells, granulocytes, dendritic cells (DCs) and macrophages.[23] Although the TGR5 expression level is low in hepatocytes, it is highly expressed in Kupffer cells-hepatic resident macrophages.[24,25] The effect of TGR5 activation or deactivation depends on the tissue where it is expressed.

Similar to other GPCRs, TGR5 expression has a positive correlation with its functional activation.[26] Thereby, the TGR5 expression dynamically changes in response to challenging conditions, and abnormal lipid metabolism affects the expression of TGR5 and induces TGR5 dysfunction. For example, atherosclerosis reduced TGR5 expression in monocytes and macrophages in high-fat diet-fed low-density lipoprotein receptor-deficient mice.[27] A decreased expression of TGR5 in M1 macrophages was observed in patients with Vogt-Koyanagi-Harada as compared with normal controls.[28] Moreover, TGR5 agonists, that is, LCA and INT-777 treatment, increased the TGR5 expression in monocyte-derived DCs of patients with Behcet's disease.[29]

3 | TGR5 ACTIVATION INDUCES AN ANTI-INFLAMMATORY EFFECT

BAs are pleiotropic metabolites that regulate inflammation via direct interactions with both germline-encoded cellular receptors and luminal bacteria.[30] However, BAs are highly pro-inflammatory and cytotoxic when dysregulated due to their detergent-like activities. TGR5 as a BA receptor, its activation has anti-inflammatory properties and induces a tolerogenic state in various systems to prevent chronic inflammation (Table 1).[31–35] In the digestive system, TGR5 deficiency exacerbated liver damage and showed steatosis and inflammation, regardless of chemicals used for model construction.[36] Besides, TGR5 agonists decreased the trafficking of immune cells into the central nervous system.[37] The cardiovascular system also took advantage of TGR5 activation which attenuated atherosclerosis and improved cell proliferation in the heart.[38] In addition, TGR5 agonists could alleviate kidney inflammation,[39] as well as alopecia areata.[40] In short, the development of TGR5 agonists has broad application prospects.

Due to the enrichment of immune cells, the role of TGR5 in enterohepatic circulation is taken as an instance for mechanism explanation. The anti-inflammatory effect of TGR5 in enterohepatic circulation protects the host from over-immunity by inhibiting the immune activation induced by antigens.[41]

3.1 | TGR5 activation regulates the polarization of macrophages

TGR5 activation promotes the conversion of macrophage from pro-inflammatory M1 phenotype to anti-inflammatory M2 phenotype.[42] In a steady state, Kupffer cells are at an M0 state (nonactivated, $CD68^+$; Figure 1).[43,44] When bacteria enter the liver along the circulation, their surface antigen activates macrophages and induces the production of pro-inflammatory cytokines, that is, interferon-gamma (IFN-γ), interleukin-1β (IL-1β), interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α), which polarize M0 macrophages towards a pro-inflammatory M1 phenotype (classical activation), marked with CD80 and CD86.[45,46]

However, hepatocyte damage-activated chronic inflammation can exacerbate hepatic injury. To protect the liver from additional damage, activated TGR5 in Kupffer cells contributes to priming $Foxp3^+$ T-regulatory cells to maintain immunologic tolerance.[47] When TGR5 is activated, the phagocytosis of antigens triggers Kupffer cells to switch from pro-inflammatory and profibrotic M1 macrophages to anti-inflammatory and antifibrotic M2 macrophages (selective activation).[48,49] M2 macrophages produce high concentrations of anti-inflammatory cytokines, such as IL-10 and transforming growth factor β (TGF-β), and are marked by CD115, CD206 and CD163.[50,51]

3.2 | TGR5 activation regulates the distribution of immune cells

Most macrophage populations originate from embryonic haematopoiesis, while a few derive from monocytes.[52]

13653083, 2024, 4, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/sji.13361, Wiley Online Library on [21/11/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 1 The discovery of TGR5 function chronologically.

Years	Potential effect
2023	TGR5 up-regulation participates in human placental mesenchymal stem cell transplantation-relieved primary sclerosing cholangitis.[123]
2022	TGR5 KO or inhibition leads to more abundant pro-inflammatory subtype of macrophages and suppressed tumour progression in NSCLC[65]; TGR5 activation ameliorates motor deficits and cognitive impairment in a subchronic Parkinson's disease mouse model[124]; and DCA induces gastric intestinal metaplasia by activating TGR5/STAT3/KLF5 axis.[125]
2021	Tgr5 KO mice show greater steatosis and inflammation by increasing liver macrophages recruitment[59]; Tgr5 KO mice show decreased hair area and length, skin thickness, and the ratio of anagen and telogen, collagen, and mast cell number and loss the bone mass than WT group. INT777 treatment improves the appearance of alopecia areata and bone microstructure in WT mice.[40]
2020	Tgr5 KO mice exhibit exacerbated liver damage, increase levels of pro-inflammatory factors and hepatic fibrosis, and enhance M1 macrophage polarization[36,71]; TGR5 agonist modulates the chemokine CCL2/CCR2[53]; Tgr5 KO obese mice exhibit no loss towards the attraction for lipids and show high daily food/energy intake, fat mass and inflammatory status[15]; overexpression of TGR5 improves cell proliferation and alleviates apoptosis rate in the heart[38]; TGR5 KO macrophages are more susceptible to LPS stimulation than WT control, and TGR5 activation suppresses LPS-induced pro-inflammatory responses in bone marrow-derived macrophages[71]; and TGR5 deficiency accelerates cholestasis and parental nutrition-associated liver disease which is involved with microbiome.[126]
2019	TGR5 deficiency impairs innate antiviral immunity.[127]
2018	TGR5 agonist leads to beige adipocyte and increases mitochondrial content in the subcutaneous WAT[17]; TGR5 activation protects host cells from vesicular stomatitis virus (VSV), Newcastle disease virus (NDV) and herpes simplex virus type 1 (HSV-1) infection.[128]
2017	Tgr5 KO mice alleviate hepatic lipid accumulation by increasing hepatic fatty acid oxidation rate and decreasing hepatic fatty acid uptake[118]; TGR5 agonist increases the weight of epididymal WAT and BAT functionality and promotes energy expenditure[84]; TGR5 agonist down-regulates TNF-α and IL-6 expression but up-regulates IL-10 expression in macrophage from bone marrow[129]; TGR5 KO enhances the recruitment of macrophages in the colonic lamina propria and worsens the severity of inflammation since TGR5 agonist reverses intestinal inflammation[50]; Tgr5 KO promotes hepatocellular apoptosis and neutralizes ischemic preconditioning-related liver protection[129]; TGR5 agonist increases microglia/macrophages but reduces pro-inflammatory microglia/macrophages in the hippocampus[130]; and TGR5 antagonizes kidney inflammation and kidney cancer cell proliferation and migration.[39]
2016	Tgr5 KO mice reduce cholangiocyte proliferation, which is elevated with TGR5 agonist[33]; TGR5 agonist attenuates hypoxia/reoxygenation-induced hepatocellular apoptosis[131]; and TGR5 agonist decreases proteinuria, podocyte injury, mesangial expansion, fibrosis and CD68 macrophage infiltration. Also, TGR5 activation induces mitochondrial biogenesis and prevents renal oxidative stress and lipid accumulation.[83]
2015	TGR5 KO is much more susceptible to LPS-induced acute gastric inflammation[132]; the itching response to intradermal injection of TGR5 agonists desensitizes rapidly and is deactivated in models of cholestasis[87]; and basal metabolic rate was ~25% higher in WT cholecystectomized mice, whereas no changes were detected in Tgr5 KO mice.[121]
2014	Adipose tissue lacking macrophage Tgr5 reveals enhanced inflammation, increased chemokine expression, higher macrophage numbers and impaired insulin responsiveness[70]; TGR5 agonist reduces clinical score which correlated with reduced monocyte and microglial activation and reduced trafficking of monocytes and T cells into the CNS[37]; and TGR5 agonists inhibit the secretion of the pro-inflammatory cytokines but not the anti-inflammatory cytokines in monocytes. TGR5 agonist inhibits TNF-α and IL-12 release in blood.[34]
2013	Scratching is reduced in Tgr5 KO mice but exacerbated inTgr5-Tg mice compared with WT mice[86]; TGR5 is highly expressed in intestinal metaplastic cells and gastric adenocarcinoma cells, and the expression level of TGR5 is no difference between intestinal metaplasia and gastric adenocarcinoma (intestinal type)[133]; and TGR5 agonism increases endothelial NO synthase(ser1177) phosphorylation in human umbilical vein endothelial cells and also inhibited lipopolysaccharide-induced monocyte adhesion to mesenteric venules in vivo.[56]
2011	Tgr5 KO mice show more severe liver necroses and inflammation, while TGR5 agonist inhibits the expression of inflammatory mediators[134]; TGR5 KO increases intestinal permeability and susceptibility to develop severe colitis, while TGR5 ligand abrogates signs and symptoms of colitis[58]; and TGR5 activation attenuated atherosclerosis with decreased intraplaque inflammation and less plaque macrophage content in Ldlr KO Tgr5 WT mice but not in Ldlr/Tgr5 double-knockout mice.[55]
2010	Tgr5 KO male mice display increased hepatic steatosis, improved insulin sensitivity with chow diet, but impaired insulin sensitivity with HFD; Tgr5 female KO mice exhibit improved insulin sensitivity when fed with HFD; and female Tgr5 KO mice have significantly lower plasma cholesterol and triglyceride levels on both diets.[135] TGR5 agonist increases gallbladder volume[136]; TGR5 is a novel neurosteroid receptor with implications for the pathogenesis of hepatic encephalopathy.[137]
2009	TGR5 agonists induce GLP-1 release, leading to improved liver and pancreatic function and enhanced glucose tolerance.[19]
2006	Tgr5 KO mice do not form cholesterol gallstones.[119]

13653083, 2024, 4, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/sji.13361, Wiley Online Library on [21/11/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

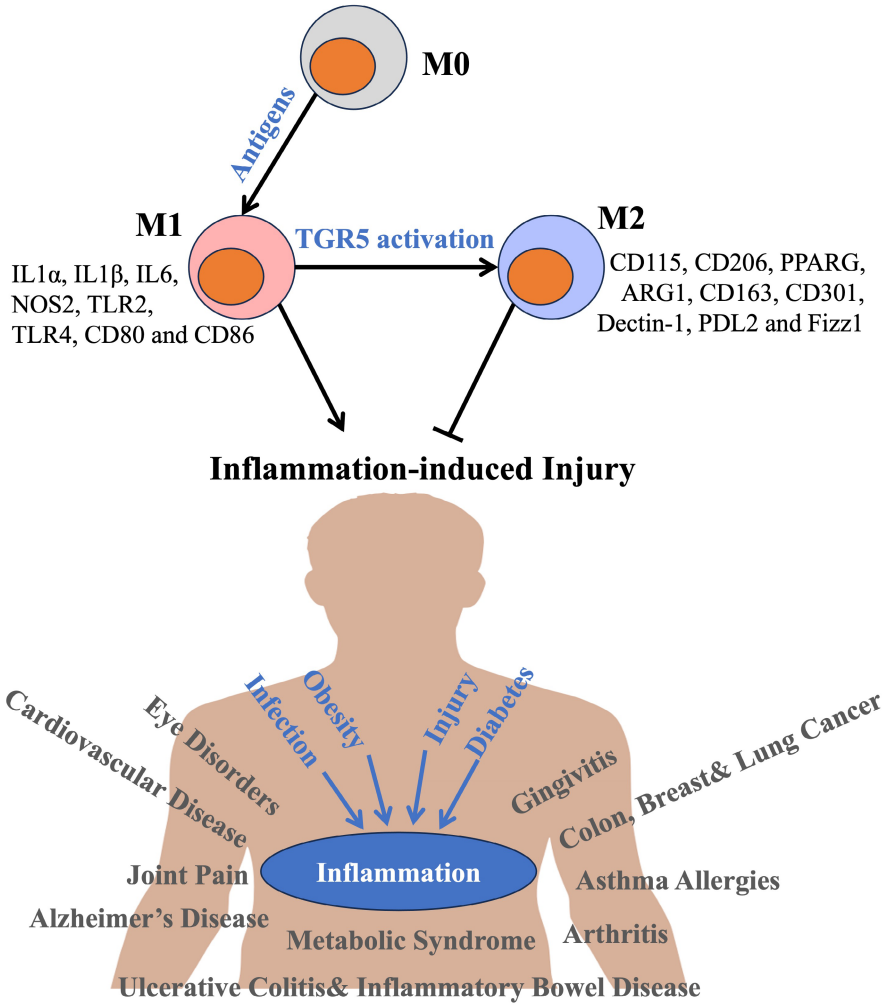

FIGURE 1 The polarization of macrophages regulates inflammation-induced injury.

During the inflammatory response, the M1 macrophage induces the up-regulation of chemokines CCL2, which attracts monocytes and macrophages from the blood to inflamed sites.[53] On the contrary, TGR5 activation stimulates the release of IL-10 and reduces CCL2, inhibiting the recruitment of monocytes and macrophages.[54] It was reported that TGR5 activation reduced the accumulation of macrophages in aortic plaques and adipose tissues in *Ldlr*$^{-/-}$ mice.[55] Moreover, TGR5 activation impaired monocyte function and reduced the monocyte adhesion in vascular endothelial cells in response to inflammation.[56,57] Activated TGR5 also regulated leukocyte trafficking in the spleen of experimental colitis mice models.[58]

Nevertheless, TGR5 deficiency increased macrophage recruitment to the liver but did not increase the pro-inflammatory phenotype of hepatic macrophages in alcohol-fed mice.[59] Rivollier et al. reported that after circulating monocytes entered the tissues, that is, the liver, TGR5 activation did not further affect the differentiation of monocyte-derived macrophages.[60] It appears that the fate of immune cells is determined earlier than previously thought.[61]

3.3 | TGR5 activation inhibits the adaptive immune response

Even though the expression of TGR5 is low in lymphoid cells, it shows indirect regulation of adaptive immunity.[62] DCs are professional antigen-presenting cells critical for the function of the adaptive immune system via their ability to prime naive T cells.[63] DCs differentiated with TGR5 agonists showed an IL-12 hypo-producing phenotype.[64] And TGR5 activation inhibited the activation of CD11c^{+} DCs (MHC class II) to attenuate the severity of experimental autoimmune uveitis.[63] Also, TGR5 activation inhibited glutathione production and induced oxidative stress, which led to apoptosis and autophagy in DCs.[29]

As a result, TGR5 activation increases the production of FoxP3^{+} regulatory T cells and reduces the production of effector T cells.[54] For instance, TGR5 activation of tumour-associated macrophages mediated CD8^{+} T-cell suppression, while TGR5 activation of macrophages co-cultured with CD4^{+} T cells inhibited Th1 and Th17 polarization, as well as the release of IFN-γ and IL-17 in the culture supernatant.[28,65] Besides, LCA-induced TGR5 activation

13653083, 2024, 4, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/sji.13361, Wiley Online Library on [21/11/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

increased the recruitment of NK cells but reduced the activation of NKT cells in liver fibrosis.[66] Correspondingly, *Tgr5* gene-ablated mice were more disease-prone than congenic littermates and had enhanced recruitment of pro-inflammatory cells, not only myeloid cells but also T cells and NKT cells.[67]

4 | TGR5 ACTIVATION MEDIATES THE *NF-kB* SIGNALLING PATHWAY AND THE ASSEMBLY OF NLRP3 INFLAMMASOME

4.1 | The anti-inflammatory effect of TGR5 is mediated by inhibiting the NF-kB signalling pathway

TGR5 binds to the Gs protein and subsequently activates the adenylyl cyclase (AC)/cyclic AMP (cAMP)/protein kinase A (PKA) signalling pathway (Figure 2).[68] PKA mediates the phosphorylation of cAMP response element-binding protein (CREB) and protein kinase B (AKT). The phosphorylation of CREB mediates repression of NF-κB-responsive elements by a signal transducer and activator of transcription 1 (STAT1)-dependent mechanism.[69] AKT phosphorylation leads to an increase of liver inhibitory protein (LIP), mediated by mTOR.[70] Increased LIP binding to DNA inhibits the transcription of numerous genes coding for chemokines and blunt NF-κB-dependent gene expression.[8]

Furthermore, TGR5 interacts with Gsk-3β, disrupting the stability of the β-catenin destruction complex. Activated PI3K/AKT following the β-catenin signalling pathway inhibits the TLR4/NF-κB pathway and subsequently attenuates the inflammatory responses.[38,71] Also, TGR5 activation promotes the β-catenin2 binding to IκBα, a substrate of the IκB kinase (IKK), and suppresses IκBα phosphorylation and p65 translocation subsequently, which inhibits the activation of the NF-κB signalling pathway in inflammatory diseases and cancer.[72] The signal transducer and activator of transcription 3 (STAT3) is also a key player in inflammation and cancer since TGR5 activation promotes STAT3 phosphorylation.[39]

4.2 | TGR5 activation affects the assembly of the NLRP3 inflammasome

TGR5 ligand binding leads to cAMP-PKA-dependent phosphorylation of NLRP3 at Ser295 in humans (Ser291 in mice). This phosphorylation promotes NLRP3 ubiquitination thus preventing the assembly of the NLRP3 inflammasome, leading to reduced production of pro-inflammatory mediators.[73] Knockdown of TGR5 increased the accumulation of cleaved caspase-8 and NLRP3, abolishing the anti-inflammatory effects of INT-777 after

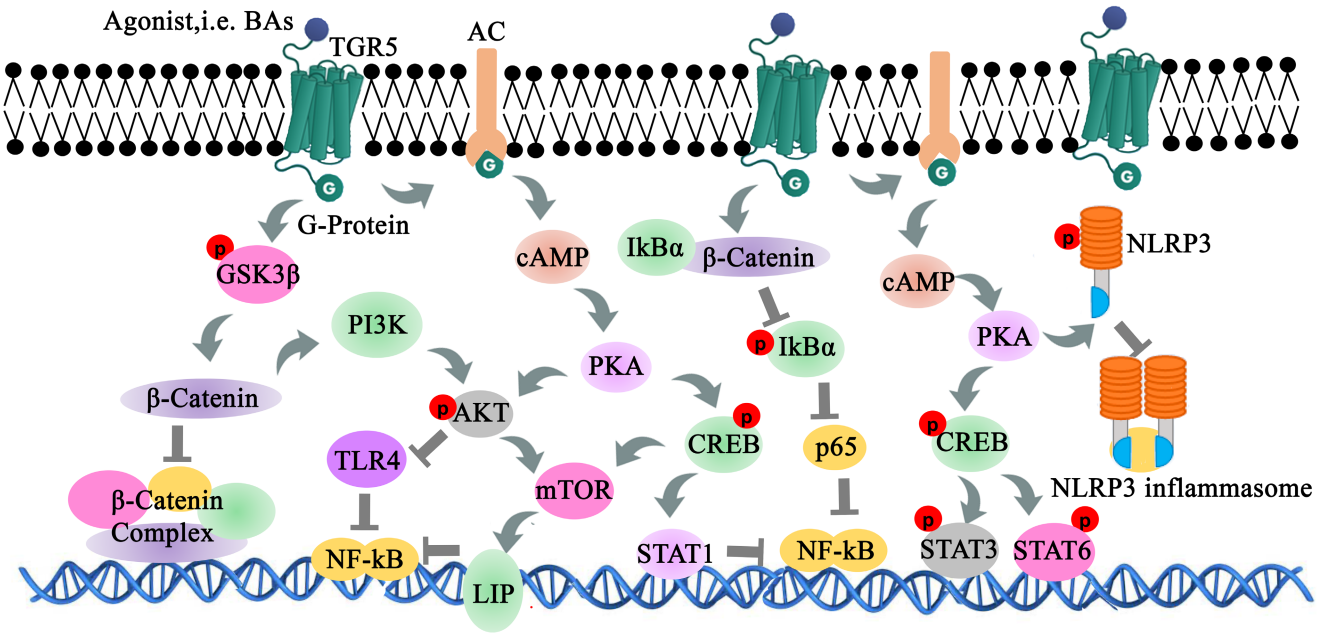

FIGURE 2 Signalling pathways participated in the anti-inflammatory effect of TGR5. AC, adenylyl cyclase; AKT, protein kinase B; cAMP, cyclic AMP; CREB, cAMP response element-binding protein; GSK3b, glycogen synthase kinase-3 β; IκBa, inhibitor a of NF-κB; LIP, liver inhibitory protein; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor kappa-B; NLRP3, NOD-like receptor protein 3; PI3K, phosphoinositide 3-kinase; PKA, protein kinase A; STAT3, signal transducer and activator of transcription 3; TLR4, toll-like receptor 4.

13653083, 2024, 4, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/sji.13361, Wiley Online Library on [21/11/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

the middle cerebral artery occlusion.[74] However, CDCA induced NLRP3 inflammasome activation and secretion of pro-inflammatory cytokine-IL-1β in macrophages through the TGR5/EGFR signalling pathway. ERK1/2, AKT and JNK are three major signalling cascade downstream of EGFR that activate NLRP3 inflammasome and initiate liver inflammation during cholestasis caused by bile duct ligation.[75] Considering CDCA is a weak agonist for TGR5 and taurocholic acid (TCA), a physiologic ligand for TGR5, fails to elicit a pro-inflammatory effect, the role of TGR5 in this pathway needs more validation. Since TGR5 deletion does not suppress IL-1β secretion totally, it suggests that BAs activate NLRP3 inflammasome acting as damage-associated molecular patterns (DAMPs) to some extent.[54]

5 | THE CLINICAL APPLICATION OF TGR5 AGONISTS AND ANTAGONISTS HAS NOT YET BEEN ACHIEVED

TGR5 participates in the regulation of multiple cellular signalling pathways, and its agonists are effective in alleviating inflammation, metabolic syndrome and digestive disorders.[76,77] TGR5 agonists include natural compounds, semisynthetic compounds and synthetic ligands.[78] Apart from BAs, certain bile alcohols function as the ligands of TGR5, which depends on the conformation of the steroidal nucleus and the position and number of the hydroxyl substituent in the side chain.[79,80] Moreover, triterpenoid compounds, that is, betulinic acid, oleanolic acid and ursolic acid, exhibit selective TGR5 agonist activity.[81] Steroid hormones, such as pregnanediol and 5α-pregnanediol, also activate TGR5 with a high affinity.[13]

INT-777 and BAR501 are potent TGR5 agonists, and their therapeutic roles have been widely studied in animal models.[82] INT-777 attenuated kidney inflammation and immune dysfunction-induced fibrosis in high-fat diet (HFD)-induced obesity mice.[83] It also ameliorated neuroinflammation via the TGR5/cAMP/PKA signalling pathway in the endovascular perforation-induced subarachnoid haemorrhage model.[73] BAR501 or BAR502 (FXR and TGR5 agonist) could reverse liver steatosis and fibrosis scores and shift macrophage polarization from an M1 to M2 phenotype in HFD-fructose-induced NASH mouse models.[84,85] TGR5 activated by BAR501 reversed intestinal inflammation by reducing the trafficking of $Ly6C^+$ monocytes from blood to intestinal mucosa.

Although TGR5 shows potent efficacy in the treatment of diseases, there is no TGR5 agonist used in the clinic so far. One concern is that, as a mediator involved in the signalling of bile acid-induced itching, TGR5 activation likely has pruritogenic effects.[82,86] However, the pruritogenic role of TGR5 may be overestimated. The pruritogenic response induced by TGR5 agonists could be reduced by 50% when animals are rapidly challenged with a second dose of the same agonist.[87] Also, betulinic acid, a TGR5 ligand, did not induce spontaneous itching in the chemical-induced cholestasis mouse model, which might be due to the dysregulation of TGR5 signalling.[87,88] Additionally, bile acid-induced itch in humans is TGR5-independent and the itch-related role of TGR5 is replaced by MRGPRX4 to some degree.[89]

Another concern is that the ubiquitous expression of TGR5 makes it hard to produce organ-specific effects. The systemic exposure of TGR5 agonist induces systemic release of glucagon-like peptides (GLPs) that cause unwanted side effects, that is, gallbladder filling. Since GLP-2 promotes gallbladder refilling via a TGR5-independent, GLP-2R-dependent pathway, other GLPs are responsible for this side effect here.[90] Novel TGR5 agonists, such as OL3, could reduce side effects through a dual function in lowering blood glucose,[91] while RDX8940, designed to have minimal systemic effects, did not inhibit gallbladder emptying.[92] Meanwhile, TGR5 overexpression promotes hepatoprotection against BA overload.[93]

Unlike the broad spectrum of agonists recognized by TGR5, only a few antagonists have been identified. SBI-115 is a TGR5 antagonist that restrains macrophage M2 polarization through the cAMP–STAT3/STAT6 signalling pathway.[65] It also reduced the proliferation and cyst growth in cultured cholangiocytes, indicating the potential role of TGR5 inhibition in the treatment of polycystic liver disease.[94] Triamterene inhibited TGR5-induced GLP-1 secretion in a dose-dependent way.[95] However, its specificity needs to be improved because triamterene induces autophagic degradation of lysosomes in a TGR5-independent way.[96]

6 | TGR5 PLAYS A COMPLICATED ROLE IN CANCER TREATMENT

Of note, TGR5-related anti-inflammatory activity is not always protective; instead, long-term activation of TGR5 may impede the treatment of liver diseases and cancers.[65,66] TGR5 gene expression is higher in most cancers compared with normal controls, that is, glioblastoma multiforme, kidney renal papillary cell carcinoma, lower-grade glioma, thymoma and uveal melanoma. The high gene expression is associated with poor prognosis. Nevertheless, the lower expression of TGR5 is linked with poor prognosis in cervical squamous cell carcinoma and endocervical adenocarcinoma, malignant mesothelioma, sarcoma and skin cutaneous melanoma.[97] TGR5

13653083, 2024, 4, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/sji.13361, Wiley Online Library on [21/11/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

deficiency activated antitumor immunity in non-small cell lung cancer via restraining M2 macrophage polarization.[65] Since TGR5 activation inhibits immune response, we are wondering whether TGR5 activation decreases the efficacy of immunotherapy on cancers.[98]

TGR5 could regulate immunotherapy indirectly by affecting microbiota and BA composition.[99] TGR5 deficiency induced dysbiosis, and the transplantation of Tgr5-KO intestinal microbiota to WT mice was sufficient to worsen alcohol-induced liver inflammation.[59,100] Moreover, gut microbiota composition could affect the response to anticancer immunotherapy by CTLA-4 blockade in sarcoma, melanoma and colon cancer.[101] Antibiotic treatment inhibited the efficacy of anti-PD1/PD-L1 therapy on non-small cell lung carcinoma, renal cell carcinoma, colorectal cancer, melanoma and urothelial carcinoma.[102–105] HCC patients who were responsive to anti-PD-1 immunotherapy have higher taxa richness in faecal samples compared with non-responders.[106,107] In addition, TGR5 deficiency affects bile acid homeostasis and the abnormal TGR5-induced dysbiosis changes the modification of 5% BAs.[108,109] Secondary BAs, that is, DCA, promoted obesity-associated liver cancer through PGE2-mediated suppression of antitumor immunity.[110] Nanoemulsion-loaded obeticholic acid (OCA) triggered NKT cell-mediated immunotherapy in the H22 orthotopic model.[111]

7 | SUMMARY AND FUTURE PERSPECTIVE

TGR5 as a therapeutic target is expected to benefit diverse diseases since it is involved in metabolic expenditure, BAs homeostasis, gut motility and inflammatory response.[14,112] Particularly, it is highly expressed in immune cells and exerts an anti-inflammatory effect by regulating cell migration and polarization, as well as the production of inflammatory mediators (cytokines and chemokines). Moreover, it participates in osteoclast differentiation, the Rap1 signalling pathway, the regulation of hormone secretion, the metabolism of steroids and so on. However, regardless of the broad application scope, there is no drug targeting TGR5 in the clinic so far. Several questions need to be answered.

The dual regulation of TGR5 on immunity and metabolism is elusive. TGR5 is a BA receptor highly expressed at the interface of the host immune system with the intestinal microbiota, determining its complicated role in metabolism and immune response.[113,114] TGR5 activation could modulate effective functions of myeloid cells,[64,115] and low-grade inflammation contributes to the development of metabolic syndrome.[116] It is difficult to define the site-specific effect of TGR5 activation, as well as the related mechanism.

Some observations about TGR5 in different physiological or pathological conditions were inconsistent. For instance, the effect of TGR5 on BA pool size and composition was still controversial. Maruyama et al. reported decreased total bile acid pool size in Tgr5 KO male and female mice at 13–14 weeks old compared with that of the WT C57BL/6N mice.[117] Tgr5 KO male mice switched the classic bile acid synthesis pathway to generate a hydrophobic bile acid pool under both free-fed and fast conditions at 20–21 weeks old, compared with WT male C57BL/6J mice.[118] However, Vessileva et al. found that Tgr5 KO mice had no significant difference in the level of cholesterol, BAs or any other bile constituents compared with healthy littermates in a hybrid background at 6–12 weeks old.[119] Ferrell et al. mentioned that the total bile acid pool size was unchanged in Tgr5 KO male mice at 4 months old, compared with male C57BL/6J mice.[120] Since the strain, age and sex of mice are different in each experiment, adding the biological clock has a significant effect on bile acid synthesis and it is hard to conclude now.[121]

The role of TGR5 in the niche or tumour-associated microenvironment is unknown, which may affect the trafficking, proliferation and differentiation of immune cells. Keitel et al. reported that TGR5 expression in liver endothelial cells contributed to the regulation of endothelial/monocyte interactions at the sinusoidal interface.[55,122] However, more studies are required to clarify the role of TGR5 in the niche. In summary, this review emphasizes the anti-inflammatory effect of TGR5 in various organs, elucidates the molecular mechanism introduces commercially available chemicals and more possible roles of TGR5 in disease treatment. It also discusses existing concerns, aiming to provide an in-depth understanding of TGR5 regulating immunity, as a prerequisite for developing TGR5 to be a pharmaceutical target.

AUTHOR CONTRIBUTIONS

DY and XH compiled the main body of manuscript, and JH helped to refine part of the manuscript. All authors read and approved the final manuscript.

ACKNOWLEDGEMENTS

Thanks to Prof. Yu-Jui Yvonne Wan for participating in the manuscript refinement.

FUNDING INFORMATION

This research was supported by the First Affiliated Hospital of Wenzhou Medical University Fund Project (2022QD040).

13653083, 2024, 4, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/sji.13361, Wiley Online Library on [21/11/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Xiaofei He https://orcid.org/0000-0002-5928-9465

REFERENCES

1. Li Y, Cheng K-C, Cheng J-T. GPR119 and GPR131: Functional difference? *Curr Res Diabet Obes J*. 2017;1(4):555566.
2. Kawamata Y, Fujii R, Hosoya M, et al. A G protein-coupled receptor responsive to bile acids. *J Biol Chem*. 2003;278(11):9435-9440.
3. Maruyama T, Miyamoto Y, Nakamura T, et al. Identification of membrane-type receptor for bile acids (M-BAR). *Biochem Biophys Res Commun*. 2002;298(5):714-719.
4. Alhadeff R, Vorobyov I, Yoon HW, Warshel A. Exploring the free-energy landscape of GPCR activation. *Proc Natl Acad Sci USA*. 2018;115(41):10327-10332.
5. Hill SJ. G-protein-coupled receptors: past, present and future. *Br J Pharmacol*. 2006;147(Suppl 1):S27-S37.
6. Pols TW, Noriega LG, Nomura M, Auwerx J, Schoonjans K. The bile acid membrane receptor TGR5: a valuable metabolic target. *Dig Dis*. 2011;29(1):37-44.
7. Wang H, Chen J, Hollister K, Sowers LC, Forman BM. Endogenous bile acids are ligands for the nuclear receptor FXR/BAR. *Mol Cell*. 1999;3(5):543-553.
8. Fiorucci S, Baldoni M, Ricci P, Zampella A, Distrutti E, Biagioli M. Bile acid-activated receptors and the regulation of macrophages function in metabolic disorders. *Curr Opin Pharmacol*. 2020;53:45-54.
9. Parks DJ, Blanchard SG, Bledsoe RK, et al. Bile acids: natural ligands for an orphan nuclear receptor. *Science*. 1999;284(5418):1365-1368.
10. Devkota S, Wang Y, Musch MW, et al. Dietary-fat-induced taurocholic acid promotes pathobiont expansion and colitis in Il10−/− mice. *Nature*. 2012;487(7405):104-108.
11. Duboc H, Rajca S, Rainteau D, et al. Connecting dysbiosis, bile-acid dysmetabolism and gut inflammation in inflammatory bowel diseases. *Gut*. 2013;62(4):531-539.
12. Makishima M, Okamoto AY, Repa JJ, et al. Identification of a nuclear receptor for bile acids. *Science*. 1999;284(5418):1362-1365.
13. Sato H, Macchiarulo A, Thomas C, et al. Novel potent and selective bile acid derivatives as TGR5 agonists: biological screening, structure-activity relationships, and molecular modeling studies. *J Med Chem*. 2008;51(6):1831-1841.
14. Guo C, Chen WD, Wang YD. TGR5, not only a metabolic regulator. *Front Physiol*. 2016;7:646.
15. Bensalem A, Murtaza B, Hichami A, et al. Bile acid receptor TGR5 is critically involved in preference for dietary lipids and obesity. *J Nutr Biochem*. 2020;76:108298.
16. Ding L, Yang Q, Zhang E, et al. Notoginsenoside Ft1 acts as a TGR5 agonist but FXR antagonist to alleviate high fat diet-induced obesity and insulin resistance in mice. *Acta Pharm Sin B*. 2021;11(6):1541-1554.
17. Velazquez-Villegas LA, Perino A, Lemos V, et al. TGR5 signalling promotes mitochondrial fission and beige remodelling of white adipose tissue. *Nat Commun*. 2018;9(1):245.
18. Watanabe M, Houten SM, Mataki C, et al. Bile acids induce energy expenditure by promoting intracellular thyroid hormone activation. *Nature*. 2006;439(7075):484-489.
19. Thomas C, Gioiello A, Noriega L, et al. TGR5-mediated bile acid sensing controls glucose homeostasis. *Cell Metab*. 2009;10(3):167-177.
20. Zhang F, Xiao X, Li Y, et al. Therapeutic opportunities of GPBAR1 in cholestatic diseases. *Front Pharmacol*. 2021;12:805269.
21. Duboc H, Tache Y, Hofmann AF. The bile acid TGR5 membrane receptor: from basic research to clinical application. *Dig Liver Dis*. 2014;46(4):302-312.
22. Tang Z, Li C, Kang B, Gao G, Li C, Zhang Z. GEPIA: a web server for cancer and normal gene expression profiling and interactive analyses. *Nucleic Acids Res*. 2017;45(W1):W98-w102.
23. Malhi H, Camilleri M. Modulating bile acid pathways and TGR5 receptors for treating liver and GI diseases. *Curr Opin Pharmacol*. 2017;37:80-86.
24. Holter MM, Chirikjian MK, Briere DA, et al. Compound 18 improves glucose tolerance in a hepatocyte TGR5-dependent manner in mice. *Nutrients*. 2020;12(7):2124.
25. Keitel V, Donner M, Winandy S, Kubitz R, Haussinger D. Expression and function of the bile acid receptor TGR5 in Kupffer cells. *Biochem Biophys Res Commun*. 2008;372(1):78-84.
26. de Ligt RA, Kourounakis AP, IJzerman AP. Inverse agonism at G protein-coupled receptors: (patho)physiological relevance and implications for drug discovery. *Br J Pharmacol*. 2000;130(1):1-12.
27. Cochain C, Vafadarnejad E, Arampatzi P, et al. Single-cell RNA-seq reveals the transcriptional landscape and heterogeneity of aortic macrophages in murine atherosclerosis. *Circ Res*. 2018;122(12):1661-1674.
28. Yang J, Hu J, Feng L, et al. Decreased expression of TGR5 in Vogt-Koyanagi-Harada (VKH) disease. *Ocul Immunol Inflamm*. 2020;28(2):200-208.
29. Hu J, Zhang Y, Yi S, et al. Lithocholic acid inhibits dendritic cell activation by reducing intracellular glutathione via TGR5 signaling. *Int J Biol Sci*. 2022;18(11):4545-4559.
30. Chen ML, Takeda K, Sundrud MS. Emerging roles of bile acids in mucosal immunity and inflammation. *Mucosal Immunol*. 2019;12(4):851-861.
31. Hylemon PB, Zhou H, Pandak WM, Ren S, Gil G, Dent P. Bile acids as regulatory molecules. *J Lipid Res*. 2009;50(8):1509-1520.
32. Finamore C, Festa C, Renga B, et al. Navigation in bile acid chemical space: discovery of novel FXR and GPBAR1 ligands. *Sci Rep*. 2016;6:29320.
33. Reich M, Deutschmann K, Sommerfeld A, et al. TGR5 is essential for bile acid-dependent cholangiocyte proliferation in vivo and in vitro. *Gut*. 2016;65(3):487-501.
34. Hogenauer K, Arista L, Schmiedeberg N, et al. G-protein-coupled bile acid receptor 1 (GPBAR1, TGR5) agonists reduce the production of proinflammatory cytokines and stabilize the alternative macrophage phenotype. *J Med Chem*. 2014;57(24):10343-10354.
35. Younossi ZM, Loomba R, Rinella ME, et al. Current and future therapeutic regimens for nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. *Hepatology*. 2018;68(1):361-371.

13653083, 2024, 4, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/sji.13361, Wiley Online Library on [21/11/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

36. Shi Y, Su W, Zhang L, et al. TGR5 regulates macrophage inflammation in nonalcoholic steatohepatitis by modulating NLRP3 inflammasome activation. *Front Immunol*. 2020;11:609060.
37. Lewis ND, Patnaude LA, Pelletier J, et al. A GPBAR1 (TGR5) small molecule agonist shows specific inhibitory effects on myeloid cell activation in vitro and reduces experimental autoimmune encephalitis (EAE) in vivo. *PloS One*. 2014;9(6):e100883.
38. Li J, Cheng R, Wan H. Overexpression of TGR5 alleviates myocardial ischemia/reperfusion injury via AKT/GSK-3beta mediated inflammation and mitochondrial pathway. *Biosci Rep*. 2020;40(1):BSR20193482.
39. Su J, Zhang Q, Qi H, et al. The G-protein-coupled bile acid receptor Gpbar1 (TGR5) protects against renal inflammation and renal cancer cell proliferation and migration through antagonizing NF-κB and STAT3 signaling pathways. *Oncotarget*. 2017;8(33):54378-54387.
40. Zhou X, Guan Z, Jin X, et al. Reversal of alopecia areata, osteoporosis follow treatment with activation of Tgr5 in mice. *Biosci Rep*. 2021;41(7):BSR20210609.
41. Merlen G, Kahale N, Ursic-Bedoya J, et al. TGR5-dependent hepatoprotection through the regulation of biliary epithelium barrier function. *Gut*. 2020;69(1):146-157.
42. Horst AK, Neumann K, Diehl L, Tiegs G. Modulation of liver tolerance by conventional and nonconventional antigen-presenting cells and regulatory immune cells. *Cell Mol Immunol*. 2016;13(3):277-292.
43. Wahlstrom A, Sayin SI, Marschall HU, Backhed F. Intestinal crosstalk between bile acids and microbiota and its impact on host metabolism. *Cell Metab*. 2016;24(1):41-50.
44. Terada M, Horisawa K, Miura S, et al. Kupffer cells induce notch-mediated hepatocyte conversion in a common mouse model of intrahepatic cholangiocarcinoma. *Sci Rep*. 2016;6:34691.
45. Perino A, Schoonjans K. TGR5 and immunometabolism: insights from physiology and pharmacology. *Trends Pharmacol Sci*. 2015;36(12):847-857.
46. Reich M, Klindt C, Deutschmann K, Spomer L, Haussinger D, Keitel V. Role of the G protein-coupled bile acid receptor TGR5 in liver damage. *Dig Dis*. 2017;35(3):235-240.
47. Heymann F, Peusquens J, Ludwig-Portugall I, et al. Liver inflammation abrogates immunological tolerance induced by Kupffer cells. *Hepatology*. 2015;62(1):279-291.
48. Wang M, You Q, Lor K, Chen F, Gao B, Ju C. Chronic alcohol ingestion modulates hepatic macrophage populations and functions in mice. *J Leukoc Biol*. 2014;96(4):657-665.
49. Ramachandran P, Pellicoro A, Vernon MA, et al. Differential Ly-6C expression identifies the recruited macrophage phenotype, which orchestrates the regression of murine liver fibrosis. *Proc Natl Acad Sci USA*. 2012;109(46):E3186-E3195.
50. Biagioli M, Carino A, Cipriani S, et al. The bile acid receptor GPBAR1 regulates the M1/M2 phenotype of intestinal macrophages and activation of GPBAR1 rescues mice from murine colitis. *J Immunol*. 2017;199(2):718-733.
51. Raggi F, Pelassa S, Pierobon D, et al. Regulation of human macrophage M1-M2 polarization balance by hypoxia and the triggering receptor expressed on myeloid cells-1. *Front Immunol*. 2017;8:1097.
52. Liu Z, Gu Y, Chakarov S, et al. Fate mapping via Ms4a3-expression history traces monocyte-derived cells. *Cell*. 2019;178(6):1509-1525.e19.
53. Biagioli M, Carino A, Fiorucci C, et al. The bile acid receptor GPBAR1 modulates CCL2/CCR2 signaling at the liver sinusoidal/macrophage interface and reverses acetaminophen-induced liver toxicity. *J Immunol*. 2020;204(9):2535-2551.
54. Fiorucci S, Biagioli M, Zampella A, Distrutti E. Bile acids activated receptors regulate innate immunity. *Front Immunol*. 2018;9:1853.
55. Pols TW, Nomura M, Harach T, et al. TGR5 activation inhibits its atherosclerosis by reducing macrophage inflammation and lipid loading. *Cell Metab*. 2011;14(6):747-757.
56. Kida T, Tsubosaka Y, Hori M, Ozaki H, Murata T. Bile acid receptor TGR5 agonism induces NO production and reduces monocyte adhesion in vascular endothelial cells. *Arterioscler Thromb Vasc Biol*. 2013;33(7):1663-1669.
57. Leonhardt J, Haider RS, Sponholz C, et al. Circulating bile acids in liver failure activate TGR5 and induce monocyte dysfunction. *Cell Mol Gastroenterol Hepatol*. 2021;12(1):25-40.
58. Cipriani S, Mencarelli A, Chini MG, et al. The bile acid receptor GPBAR-1 (TGR5) modulates integrity of intestinal barrier and immune response to experimental colitis. *PloS One*. 2011;6(10):e25637.
59. Spatz M, Ciocan D, Merlen G, et al. Bile acid-receptor TGR5 deficiency worsens liver injury in alcohol-fed mice by inducing intestinal microbiota dysbiosis. *JHEP Rep*. 2021;3(2):100230.
60. Rivollier A, He J, Kole A, Valatas V, Kelsall BL. Inflammation switches the differentiation program of Ly6Chi monocytes from antiinflammatory macrophages to inflammatory dendritic cells in the colon. *J Exp Med*. 2012;209(1):139-155.
61. Khajuria RK, Munschauer M, Ulirsch JC, et al. Ribosome levels selectively regulate translation and lineage commitment in human hematopoiesis. *Cell*. 2018;173(1):90-103.e19.
62. Newton K, Dixit VM. Signaling in Innate Immunity and Inflammation. *Cold Spring Harb Perspect Biol*. 2012;4(3):a006049.
63. Hu J, Wang C, Huang X, et al. Gut microbiota-mediated secondary bile acids regulate dendritic cells to attenuate autoimmune uveitis through TGR5 signaling. *Cell Rep*. 2021;36(12):109726.
64. Ichikawa R, Takayama T, Yoneno K, et al. Bile acids induce monocyte differentiation toward interleukin-12 hypo-producing dendritic cells via a TGR5-dependent pathway. *Immunology*. 2012;136(2):153-162.
65. Zhao L, Zhang H, Liu X, et al. TGR5 deficiency activates antitumor immunity in non-small cell lung cancer via restraining M2 macrophage polarization. *Acta Pharm Sin B*. 2022;12(2):787-800.
66. Shao J, Ge T, Tang C, Wang G, Pang L, Chen Z. Synergistic anti-inflammatory effect of gut microbiota and lithocholic acid on liver fibrosis. *Inflamm Res*. 2022;71(10–11):1389-1401.
67. Schote AB, Turner JD, Schiltz J, Muller CP. Nuclear receptors in human immune cells: expression and correlations. *Mol Immunol*. 2007;44(6):1436-1445.
68. Okajima F. Regulation of inflammation by extracellular acidification and proton-sensing GPCRs. *Cell Signal*. 2013;25(11):2263-2271.
69. Haselow K, Bode JG, Wammers M, et al. Bile acids PKA-dependently induce a switch of the IL-10/IL-12 ratio and reduce proinflammatory capability of human macrophages. *J Leukoc Biol*. 2013;94(6):1253-1264.
70. Perino A, Pols TW, Nomura M, Stein S, Pellicciari R, Schoonjans K. TGR5 reduces macrophage migration through

13653083, 2024, 4, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/sji.13361, Wiley Online Library on [21/11/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

mTOR-induced C/EBPbeta differential translation. *J Clin Invest*. 2014;124(12):5424-5436.
71. Rao J, Yang C, Yang S, et al. Deficiency of TGR5 exacerbates immune-mediated cholestatic hepatic injury by stabilizing the β-catenin destruction complex. *Int Immunol*. 2020;32(5):321-334.
72. Xiao H, Sun X, Liu R, et al. Gentiopicroside activates the bile acid receptor Gpbar1 (TGR5) to repress NF-kappaB pathway and ameliorate diabetic nephropathy. *Pharmacol Res*. 2020;151:104559.
73. Hu X, Yan J, Huang L, et al. INT-777 attenuates NLRP3-ASC inflammasome-mediated neuroinflammation via TGR5/cAMP/PKA signaling pathway after subarachnoid hemorrhage in rats. *Brain Behav Immun*. 2021;91:587-600.
74. Liang H, Matei N, McBride DW, et al. TGR5 activation attenuates neuroinflammation via Pellino3 inhibition of caspase-8/NLRP3 after middle cerebral artery occlusion in rats. *J Neuroinflammation*. 2021;18(1):40.
75. Gong Z, Zhou J, Zhao S, et al. Chenodeoxycholic acid activates NLRP3 inflammasome and contributes to cholestatic liver fibrosis. *Oncotarget*. 2016;7(51):83951-83963.
76. Liu CW, Yang F, Cheng SZ, Liu Y, Wan LH, Cong HL. Rosuvastatin postconditioning protects isolated hearts against ischemia-reperfusion injury: the role of radical oxygen species, PI3K-Akt-GSK-3beta pathway, and mitochondrial permeability transition pore. *Cardiovasc Ther*. 2017;35(1):3-9.
77. van Nierop FS, Scheltema MJ, Eggink HM, et al. Clinical relevance of the bile acid receptor TGR5 in metabolism. *Lancet Diabetes Endocrinol*. 2017;5(3):224-233.
78. Luxenburger A, Harris LD, Ure EM, et al. The discovery of 12β-methyl-17-epi-18-nor-bile acids as potent and selective TGR5 agonists. *Eur J Med Chem*. 2023;250:115143.
79. Iguchi Y, Yamaguchi M, Sato H, Kihira K, Nishimaki-Mogami T, Une M. Bile alcohols function as the ligands of membrane-type bile acid-activated G protein-coupled receptor. *J Lipid Res*. 2010;51(6):1432-1441.
80. Portincasa P, Di Ciaula A, Garruti G, Vacca M, De Angelis M, Wang DQ. Bile acids and GPBAR-1: dynamic interaction involving genes, environment and gut microbiome. *Nutrients*. 2020;12(12):3709.
81. Genet C, Strehle A, Schmidt C, et al. Structure-activity relationship study of betulinic acid, a novel and selective TGR5 agonist, and its synthetic derivatives: potential impact in diabetes. *J Med Chem*. 2010;53(1):178-190.
82. De Marino S, Festa C, Sepe V, Zampella A. Chemistry and pharmacology of GPBAR1 and FXR selective agonists, dual agonists, and antagonists. *Handb Exp Pharmacol*. 2019;256:137-165.
83. Wang XX, Edelstein MH, Gafter U, et al. G protein-coupled bile acid receptor TGR5 activation inhibits kidney disease in obesity and diabetes. *J Am Soc Nephrol*. 2016;27(5):1362-1378.
84. Carino A, Cipriani S, Marchiano S, et al. Gpbar1 agonism promotes a Pgc-1alpha-dependent browning of white adipose tissue and energy expenditure and reverses diet-induced steatohepatitis in mice. *Sci Rep*. 2017;7(1):13689.
85. Carino A, Cipriani S, Marchiano S, et al. BAR502, a dual FXR and GPBAR1 agonist, promotes browning of white adipose tissue and reverses liver steatosis and fibrosis. *Sci Rep*. 2017;7:42801.
86. Alemi F, Kwon E, Poole DP, et al. The TGR5 receptor mediates bile acid-induced itch and analgesia. *J Clin Invest*. 2013;123(4):1513-1530.
87. Cipriani S, Renga B, D'Amore C, et al. Impaired itching perception in murine models of cholestasis is supported by dysregulation of GPBAR1 signaling. *PloS One*. 2015;10(7):e0129866.
88. Meixiong J, Anderson M, Limjunyawong N, et al. Activation of mast-cell-expressed mas-related G-protein-coupled receptors drives non-histaminergic itch. *Immunity*. 2019;50(5):1163-1171 e5.
89. Yu H, Zhao T, Liu S, et al. MRGPRX4 is a bile acid receptor for human cholestatic itch. *Elife*. 2019;8:8.
90. Yusta B, Matthews D, Flock GB, et al. Glucagon-like peptide-2 promotes gallbladder refilling via a TGR5-independent, GLP-2R-dependent pathway. *Mol Metab*. 2017;6(6):503-511.
91. Ma SY, Ning MM, Zou QA, et al. OL3, a novel low-absorbed TGR5 agonist with reduced side effects, lowered blood glucose via dual actions on TGR5 activation and DPP-4 inhibition. *Acta Pharmacol Sin*. 2016;37(10):1359-1369.
92. Finn PD, Rodriguez D, Kohler J, et al. Intestinal TGR5 agonism improves hepatic steatosis and insulin sensitivity in Western diet-fed mice. *Am J Physiol Gastrointest Liver Physiol*. 2019;316(3):G412-G424.
93. Bidault-Jourdainne V, Merlen G, Glénisson M, et al. TGR5 controls bile acid composition and gallbladder function to protect the liver from bile acid overload. *JHEP Rep*. 2021;3(2):100214.
94. Masyuk TV, Masyuk AI, Lorenzo Pisarello M, et al. TGR5 contributes to hepatic cystogenesis in rodents with polycystic liver diseases through cyclic adenosine monophosphate/Galphas signaling. *Hepatology*. 2017;66(4):1197-1218.
95. Li Y, Cheng KC, Niu CS, Lo SH, Cheng JT, Niu HS. Investigation of triamterene as an inhibitor of the TGR5 receptor: identification in cells and animals. *Drug Des Dev Ther*. 2017;11:1127-1134.
96. Park NY, Jo DS, Kim YH, et al. Triamterene induces autophagic degradation of lysosome by exacerbating lysosomal integrity. *Arch Pharm Res*. 2021;44(6):621-631.
97. Guan Z, Luo L, Liu S, et al. The role of TGR5 as an onco-immunological biomarker in tumor staging and prognosis by encompassing the tumor microenvironment. *Front Oncol*. 2022;12:953091.
98. Mahipal A, Tella SH, Kommalapati A, Lim A, Kim R. Immunotherapy in hepatocellular carcinoma: is there a light at the end of the tunnel? *Cancers (Basel)*. 2019;11(8):1078.
99. Rooks MG, Garrett WS. Gut microbiota, metabolites and host immunity. *Nat Rev Immunol*. 2016;16(6):341-352.
100. Jena PK, Sheng L, Di Lucente J, Jin LW, Maezawa I, Wan YY. Dysregulated bile acid synthesis and dysbiosis are implicated in Western diet-induced systemic inflammation, microglial activation, and reduced neuroplasticity. *FASEB J*. 2018;32(5):2866-2877.
101. Vétizou M, Pitt JM, Daillère R, et al. Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota. *Science*. 2015;350(6264):1079-1084.
102. Xu X, Lv J, Guo F, et al. Gut microbiome influences the efficacy of PD-1 antibody immunotherapy on MSS-type colorectal cancer via metabolic pathway. *Front Microbiol*. 2020;11:814.
103. Routy B, Le Chatelier E, Derosa L, et al. Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. *Science*. 2018;359(6371):91-97.
104. Sivan A, Corrales L, Hubert N, et al. Commensal Bifidobacterium promotes antitumor immunity and facilitates anti-PD-L1 efficacy. *Science*. 2015;350(6264):1084-1089.
105. Matson V, Fessler J, Bao R, et al. The commensal microbiome is associated with anti-PD-1 efficacy in metastatic melanoma patients. *Science*. 2018;359(6371):104-108.

13653083, 2024, 4, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/sji.13361, Wiley Online Library on [21/11/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

106. Zheng Y, Wang T, Tu X, et al. Gut microbiome affects the response to anti-PD-1 immunotherapy in patients with hepatocellular carcinoma. *J Immunother Cancer*. 2019;7(1):193.
107. Jena PK, Sheng L, Nagar N, et al. Synbiotics Bifidobacterium infantis and milk oligosaccharides are effective in reversing cancer-prone nonalcoholic steatohepatitis using western diet-fed FXR knockout mouse models. *J Nutr Biochem*. 2018;57:246-254.
108. Baars A, Oosting A, Knol J, Garssen J, van Bergenhenegouwen J. The gut microbiota as a therapeutic target in IBD and metabolic disease: a role for the bile acid receptors FXR and TGR5. *Microorganisms*. 2015;3(4):641-666.
109. Sheng L, Jena PK, Hu Y, et al. Hepatic inflammation caused by dysregulated bile acid synthesis is reversible by butyrate supplementation. *J Pathol*. 2017;243(4):431-441.
110. Jia B, Jeon CO. Promotion and induction of liver cancer by gut microbiome-mediated modulation of bile acids. *PLoS Pathog*. 2019;15(9):e1007954.
111. Ji G, Ma L, Yao H, et al. Precise delivery of obeticholic acid via nanoapproach for triggering natural killer T cell-mediated liver cancer immunotherapy. *Acta Pharm Sin B*. 2020;10(11):2171-2182.
112. Merlen G, Bidault-Jourdainne V, Kahale N, et al. Hepatoprotective impact of the bile acid receptor TGR5. *Liver Int*. 2020;40(5):1005-1015.
113. Lamkanfi M, Dixit VM. Mechanisms and functions of inflammasomes. *Cell*. 2014;157(5):1013-1022.
114. Guo C, Xie S, Chi Z, et al. Bile acids control inflammation and metabolic disorder through inhibition of NLRP3 inflammasome. *Immunity*. 2016;45(4):802-816.
115. Yoneno K, Hisamatsu T, Shimamura K, et al. TGR5 signalling inhibits the production of pro-inflammatory cytokines by in vitro differentiated inflammatory and intestinal macrophages in Crohn's disease. *Immunology*. 2013;139(1):19-29.
116. Olefsky JM, Glass CK. Macrophages, inflammation, and insulin resistance. *Annu Rev Physiol*. 2010;72:219-246.
117. Maruyama T, Tanaka K, Suzuki J, et al. Targeted disruption of G protein-coupled bile acid receptor 1 (Gpbar1/M-bar) in mice. *J Endocrinol*. 2006;191(1):197-205.
118. Donepudi AC, Boehme S, Li F, Chiang JY. G-protein-coupled bile acid receptor plays a key role in bile acid metabolism and fasting-induced hepatic steatosis in mice. *Hepatology*. 2017;65(3):813-827.
119. Vassileva G, Golovko A, Markowitz L, et al. Targeted deletion of Gpbar1 protects mice from cholesterol gallstone formation. *Biochem J*. 2006;398(3):423-430.
120. Ferrell JM, Pathak P, Boehme S, Gilliland T, Chiang JYL. Deficiency of both Farnesoid X receptor and Takeda G protein-coupled receptor 5 exacerbated liver fibrosis in mice. *Hepatology*. 2019;70(3):955-970.
121. Cortes V, Amigo L, Zanlungo S, et al. Metabolic effects of cholecystectomy: gallbladder ablation increases basal metabolic rate through G-protein coupled bile acid receptor Gpbar1-dependent mechanisms in mice. *PloS One*. 2015;10(3):e0118478.
122. Keitel V, Reinehr R, Gatsios P, et al. The G-protein coupled bile salt receptor TGR5 is expressed in liver sinusoidal endothelial cells. *Hepatology*. 2007;45(3):695-704.
123. Yao Q, Chen W, Yu Y, et al. Human placental mesenchymal stem cells relieve primary sclerosing cholangitis via upregulation of TGR5 in Mdr2(−/−) mice and human intrahepatic cholangiocyte organoid models. *Research (Wash D C)*. 2023;6:0207.
124. Huang R, Gao Y, Chen J, et al. TGR5 agonist INT-777 alleviates inflammatory neurodegeneration in Parkinson's disease mouse model by modulating mitochondrial dynamics in microglia. *Neuroscience*. 2022;490:100-119.
125. Jin D, Huang K, Xu M, et al. Deoxycholic acid induces gastric intestinal metaplasia by activating STAT3 signaling and disturbing gastric bile acids metabolism and microbiota. *Gut Microbes*. 2022;14(1):2120744.
126. Willis KA, Gomes CK, Rao P, et al. TGR5 signaling mitigates parenteral nutrition-associated liver disease. *Am J Physiol Gastrointest Liver Physiol*. 2020;318(2):G322-G335.
127. Hu MM, He WR, Gao P, et al. Virus-induced accumulation of intracellular bile acids activates the TGR5-beta-arrestin-SRC axis to enable innate antiviral immunity. *Cell Res*. 2019;29(3):193-205.
128. Xiong Q, Huang H, Wang N, et al. Metabolite-sensing G protein coupled receptor TGR5 protects host from viral infection through amplifying type I interferon responses. *Front Immunol*. 2018;9:2289.
129. Yang H, Zhou H, Zhuang L, et al. Plasma membrane-bound G protein-coupled bile acid receptor attenuates liver ischemia/reperfusion injury via the inhibition of toll-like receptor 4 signaling in mice. *Liver Transpl*. 2017;23(1):63-74.
130. Yanguas-Casas N, Barreda-Manso MA, Nieto-Sampedro M, Romero-Ramirez L. TUDCA: an agonist of the bile acid receptor GPBAR1/TGR5 with anti-inflammatory effects in microglial cells. *J Cell Physiol*. 2017;232(8):2231-2245.
131. Zhuang L, Fan Y, Lu L, et al. Ischemic preconditioning protects hepatocytes from ischemia-reperfusion injury via TGR5-mediated anti-apoptosis. *Biochem Biophys Res Commun*. 2016;473(4):966-972.
132. Guo C, Qi H, Yu Y, et al. The G-protein-coupled bile acid receptor Gpbar1 (TGR5) inhibits gastric inflammation through antagonizing NF-kappaB signaling pathway. *Front Pharmacol*. 2015;6:287.
133. Cao W, Tian W, Hong J, et al. Expression of bile acid receptor TGR5 in gastric adenocarcinoma. *Am J Physiol Gastrointest Liver Physiol*. 2013;304(4):G322-G327.
134. Wang YD, Chen WD, Yu D, Forman BM, Huang W. The G-protein-coupled bile acid receptor, Gpbar1 (TGR5), negatively regulates hepatic inflammatory response through antagonizing nuclear factor kappa light-chain enhancer of activated B cells (NF-kappaB) in mice. *Hepatology*. 2011;54(4):1421-1432.
135. Vassileva G, Hu W, Hoos L, et al. Gender-dependent effect of Gpbar1 genetic deletion on the metabolic profiles of diet-induced obese mice. *J Endocrinol*. 2010;205(3):225-232.
136. Li T, Holmstrom SR, Kir S, et al. The G protein-coupled bile acid receptor, TGR5, stimulates gallbladder filling. *Mol Endocrinol*. 2011;25(6):1066-1071.
137. Keitel V, Gorg B, Bidmon HJ, et al. The bile acid receptor TGR5 (Gpbar-1) acts as a neurosteroid receptor in brain. *Glia*. 2010;58(15):1794-1805.

How to cite this article: Ye D, He J, He X. The role of bile acid receptor TGR5 in regulating inflammatory signalling. *Scand J Immunol*. 2024;99:e13361. doi:10.1111/sji.13361

13653083, 2024, 4, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/sji.13361, Wiley Online Library on [21/11/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License